

# GUIDELINE for Aspergillosis

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The Aspergillosis guidelines were first published in the *J Feline Med Surg* 2013, 15: 605-610 by *Katrin Hartmann et al.* The present guidelines were updated by *Katrin Hartmann and Vanessa Barrs (University of Sidney)*.

## Synopsis

Aspergillosis is a sporadic mycosis that occurs worldwide in mammals and birds. Similar to the disease in humans, aspergillosis in cats can be classified by anatomic location, invasiveness, duration of infection, host immune status, pathology, and pathogenesis. The most common site of clinical signs is the respiratory tract, reflecting the primary inhalational route of infection. Respiratory involvement is usually confined to the upper respiratory tract, as chronic fungal rhinosinusitis (FRS). However, invasive pulmonary aspergillosis (IPA) can occur as a focal infection (Hazell et al., 2011) or as part of disseminated invasive aspergillosis (DIA) (Ossent, 1987; Burk et al., 1990). Focal infections of the ear, cornea, gastrointestinal tract, or urinary bladder have also been described (Stokes, 1973; Adamama-Moraitou et al., 2001; Labelle et al., 2009; Goodale et al., 2016).

*Aspergillus* species infections are commonly associated with predisposing local or systemic factors (Giordano et al., 2010). In contrast to dogs, in which (nasal) aspergillosis is relatively common, aspergillosis is rare in cats, but considered an emerging infection, e.g., in Australia (Barrs et al., 2013). There are two clinical forms of FRS in cats, sino-nasal aspergillosis (SNA), characterized by signs of chronic nasal infection, and the newly emerging invasive sino-orbital aspergillosis (SOA) form, characterized by signs of orbital and surrounding tissue invasion. Sino-orbital involvement has been described now in almost two-thirds of reported cases (Barrs and Talbot, 2014). Treatment should consist of local and systemic antifungal therapy.

## Agent Properties

Aspergillosis is caused by fungal organisms of the genus *Aspergillus*. *Aspergillus* species are ubiquitous saprophytes. There is some confusion in the nomenclature of these fungi because some species in the section *Fumigati* have a teleomorphic form (sexual phase), which for some years was assigned to the genus *Neosartorya*, while its anamorph (asexual phase) was assigned to the genus *Aspergillus*. These species were referred to by their teleomorph name, which had taxonomic precedence. Recently, a one-fungus-one-name principle was adopted, such that species formerly known as *Neosartorya* are now included in the genus *Aspergillus*, e.g. *Neosartorya udagawae* is now *Aspergillus udagawae* (Miller et al., 2011). Species identification only by phenotypic features has probably led to over-identification of *Aspergillus fumigatus* as an etiological agent in cats in previous reports. There are over 60 closely related species within the section *Fumigati* and at least seven of these can cause aspergillosis in cats (Table 1). These so-called "cryptic" species, including *Aspergillus felis*, *Aspergillus udagawae*, and *Aspergillus lentulus* are often misidentified by conventional methods and require molecular techniques for correct identification. Other *Aspergillus* species outside of the section *Fumigati* have also occasionally been reported to cause feline aspergillosis.

Tab. 1. *Aspergillus* species reported to cause aspergillosis in cats, based on molecular identification based on  $\beta$ -tubulin sequence ( $\geq 99\%$  homology with type strains) or ITS gene sequence (100% homology)

SECTION	SPECIES COMPLEX	SPECIES	FORM OF DISEASE IN CATS
Fumigati	<i>Aspergillus fumigatus</i>	<i>Aspergillus fumigatus</i>	SNA (Barrs et al., 2013, 2014, 2015; Taylor et al., 2016; Tamborini et al., 2016)
Fumigati	<i>Aspergillus fumigatus</i>	<i>Aspergillus lentulus</i>	SNA (Barrs et al., 2013)
Fumigati	<i>Aspergillus fumigatus</i>	<i>Aspergillus fischeri</i>	SOA (Kano et al., 2015)
Fumigati	—————	<i>Aspergillus thermomutatus</i>	SNA, SOA
Fumigati	<i>Aspergillus viridinutans</i>	<i>Aspergillus felis</i>	SNA, SOA (Barrs et al., 2013, 2014, 2015)
Fumigati	<i>Aspergillus viridinutans</i>	<i>Aspergillus udagawae</i>	SOA (Barrs et al., 2013, 2014; Kano et al., 2008, 2013)
Fumigati	<i>Aspergillus viridinutans</i>	<i>Aspergillus wyomingensis</i>	SOA (Barrs et al., 2014)
Nigri		<i>Aspergillus niger</i>	SNA (Barrs and Talbot, 2014)
Flavi		<i>Aspergillus flavus</i>	SNA (Barrs et al., 2015)
<b>SNA, SINO-NASAL ASPERGILLOSIS</b>	<b>SOA, SINO-ORBITAL ASPERGILLOSIS</b>		

There are differences in virulence and invasion ability between species (Sugui et al., 2014). Non-invasive infections are most frequently caused by *Aspergillus fumigatus*, while *Aspergillus felis* and *Aspergillus udagawae* are the most common cause of invasive infections, and severe cases commonly seem to be associated with *Neosartorya* species infections (Burk et al., 1990), but *Aspergillus flavus*, *Aspergillus nidulans*, *Aspergillus niger*, and *Aspergillus terreus* have also been detected.

## Epidemiology

*Aspergillus* species are found worldwide in soil and decaying vegetation. All mammals, including humans, are susceptible to aspergillosis. Immunosuppressed persons (e.g., allogenic bone-marrow or organ transplant patients) are particularly prone to developing the disease. Cats and other animals are infected through inhalation of environmental fungal spores. Direct transmission does not occur. Thus, aspergillosis is not a zoonosis.

Feline aspergillosis occurs worldwide. Most cases have been reported from Australia and the United States (Wilkinson et al., 1982; Hamilton et al., 2000; Tomsa et al., 2003; Whitney et al., 2005; Katz et al., 2005; McLellan et al., 2006; Furrow and Groman, 2009; Karnik et al., 2009; Smith and Hoffman, 2010; Barrs et al., 2013), but aspergillosis has also been described in the United Kingdom, Switzerland, Germany, Japan, and Italy (Tomsa et al., 2003; Schulz et al., 2007; Kano et al., 2008; Barachetti et al., 2009; Giordano et al., 2010; Kano et al., 2013; Kano et al., 2015; Tamborini et al., 2016). No age or sex predisposition has been detected, but brachycephalic breeds, especially Persian and Himalayan cats, are over-represented (Tomsa et al., 2003; Whitney et al., 2005; Barrs et al., 2015). Reduced drainage of upper respiratory secretions has been suggested as a predisposing factor. SNA and SOA occasionally occur in association with facial trauma, nasal neoplasia, or inhaled plant material, similar to what has been reported in canine SNA (Sharp et al., 1991; Peeters and Clercx, 2007; Barrs and Talbot, 2014). Additional suggested factors include innate defects of mucosal immunity, previous viral upper respiratory tract infections, and antibiotic treatment (Tomsa et al., 2003; Barrs and Talbot, 2014). No association of upper respiratory tract aspergillosis and feline retrovirus infections has been reported (Barrs et al., 2015).

Cats with SNA or SOA appear to be systemically immunocompetent, while cats with DIA are usually immunosuppressed by administration of immunosuppressive drugs or other disease, e.g., feline leukaemia virus infection, feline panleukopenia, feline infectious peritonitis, or endoparasitoses (Ossent, 1987). Diabetes mellitus, a risk factor for aspergillosis in humans, is also likely a risk

factor for feline aspergillosis, as several cases of aspergillosis with upper or lower respiratory involvement have been reported in cats with diabetes mellitus (Davies and Troy, 1996; Malik et al., 2004; Furrow and Groman, 2009; Hazell et al., 2011; Kano et al., 2015).

## Pathogenesis

Infection occurs after inhalation of environmental *Aspergillus* species conidia (spores), which are deposited in the sino-nasal cavity, the primary site of infection. SNA is generally non-invasive; fungal colonies adhere to, but do not penetrate the mucosal epithelium. By contrast, cats with SOA have extensive submucosal hyphal invasion. In SOA, the infection spreads by direct extension from the sino-nasal cavity into the orbit through lysis of the orbital or frontal bone (Barrs et al., 2014). To cause infection, the fungus must adhere to the respiratory epithelium, penetrate it, destroy surrounding cells, and resist phagocytosis. *Aspergillus* species conidia bind to various cell surface proteins using specific adhesion molecules, such as hydrophobins. *Aspergillus fumigatus* also produces an immunosuppressive toxin (gliotoxin) that inhibits macrophage phagocytosis. Other metabolites impair mucociliary action and prolong the organisms' epithelial resistance, while enzymes (e.g., proteases) help to invade tissues.

## Clinical signs

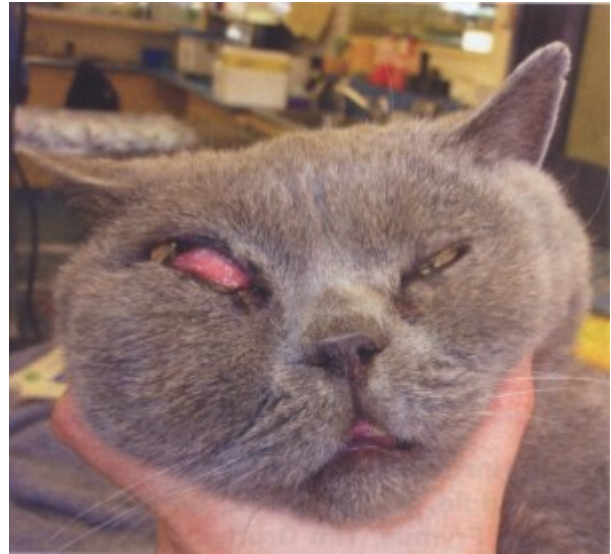
### *Upper respiratory tract aspergillosis*

SNA is characterized by local signs of chronic nasal infection, such as sneezing, uni- or bilateral serous to mucopurulent nasal discharge, and sometimes epistaxis. Stertorous breathing, granuloma formation, soft tissue masses protruding from the nares, and bone lysis are less frequent abnormalities (Tomsa et al., 2003; Whitney et al., 2005; Barrs et al., 2012).

Cats with SOA are usually presented by their owners for a "swollen eye" due to exophthalmos caused by an orbital fungal granuloma. Most also have a history of nasal discharge or sneezing, and nasal lesions as well as lysis of the orbital lamina have been identified at necropsy or using imaging techniques (Hamilton et al., 2000; Barachetti et al., 2009; Giordano et al., 2010; Barrs et al., 2012; Pilton et al., 2014). SOA is characterized by signs of orbital and surrounding tissue invasion, including unilateral exophthalmos, third eyelid prolapse (Fig. 1), conjunctival hyperaemia, and keratitis (Fig. 2.) (Hamilton et al., 2000; McLellan et al., 2006; Giordano et al., 2010). In some cases, a mass in the pterygopalatine fossa (Fig. 3), ulceration of the hard palate, or even facial distortion or skin ulcers from involvement of the paranasal tissues have been described (Smith and Hoffman, 2010; Declercq et al., 2012). The CNS can be involved leading to neurological signs, including blindness, seizures, nystagmus, circling, facial muscle fasciculation and hyperaesthesia (Giordano et al., 2010; Smith and Hoffman, 2010; Barrs et al., 2012). Regional lymphadenopathy and fever can also occur.



*Fig. 1. Exophthalmos of the left eye in a cat with a left retrobulbar fungal granuloma (sino-orbital aspergillosis). There is prolapse of the third eyelid. A partial lateral tarsorrhaphy was performed to prevent exposure keratitis (courtesy of Vanessa Barrs, University Veterinary Teaching Hospital, Sydney, Australia).*



*Fig. 2. Right exophthalmos, third eyelid prolapse and oedema and swelling of the right side of the face in a cat with a right retrobulbar and paranasal fungal granuloma (courtesy of Vanessa Barrs, University Veterinary Teaching Hospital, Sydney, Australia).*



*Fig. 3. Ventral expansion of retrobulbar fungal granulomas causes a mass effect in the pteryoplatine fossa as seen in this cat with a right retrobulbar fungal granuloma (arrow) (courtesy of Vanessa Barrs, University Veterinary Teaching Hospital, Sydney, Australia).*

### *Other forms of aspergillosis*

Atypical cases of aspergillosis have been reported, including pneumonia (Fig.4). Clinical signs in pulmonary aspergillosis and DIA are usually non-specific, e.g., anorexia, lethargy, weight loss, fever. They also can reflect specific organ involvement, e.g., dyspnoea, coughing (pulmonary aspergillosis and DIA), or CNS signs (DIA) (Ossent, 1987).

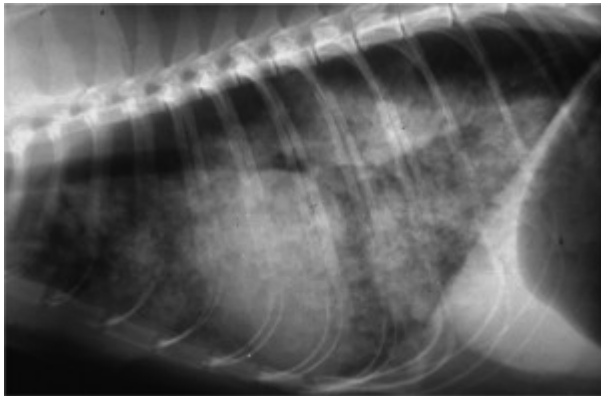


Fig. 4. Thoracic radiographs (latero-lateral view) of a cat with pulmonary aspergillosis, diagnosed at necropsy (courtesy of Katrin Hartmann, Medizinische Kleintierklinik, Ludwig-Maximilians-Universität München, Germany).

Mycotic otitis externa caused by *Aspergillus* species in cats is typically associated with a brown ceruminous otic discharge (Goodale et al., 2016). Additionally a case of pyothorax in a diabetic cat (Hazell et al., 2011), a cat with generalized systemic infection (Schulz et al., 2007), and a cat with ulcerative keratitis (Labelle et al., 2009) were reported.

## Immunity

Immunity against *Aspergillus* spp. infection is poorly understood. Many cats develop antibodies, but some cats produce only low or undetectable antibody levels (mostly in cases of *Aspergillus fumigatus* infection) (Whitney et al., 2005). Additionally, cats can produce antibodies without clinical disease which is likely the result of non-invasive mucous membrane colonization that occurs in many healthy cats.

## Diagnosis

Diagnosis is based on the demonstration of fungal hyphae by cytology or histology (Fig. 5a and b) and definitive confirmation by fungal culture (Fig. 6a and b). Detection of fungal antigen or antibodies is considered an additional diagnostic tool that can be helpful in combination with other diagnostic methods. Diagnostic imaging can be suggestive of fungal involvement.

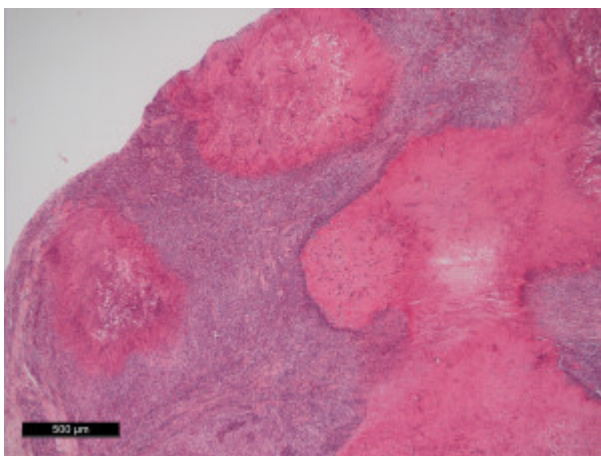
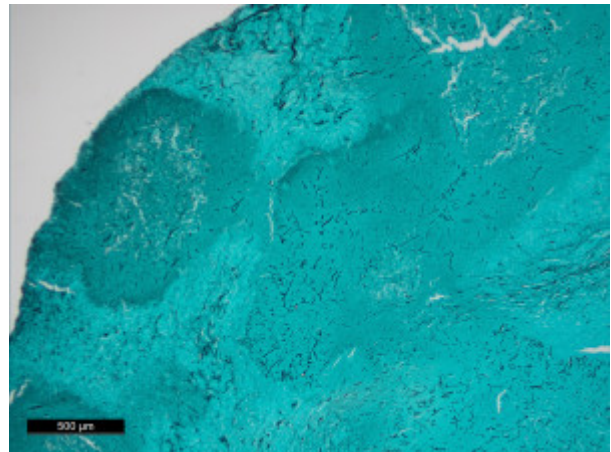
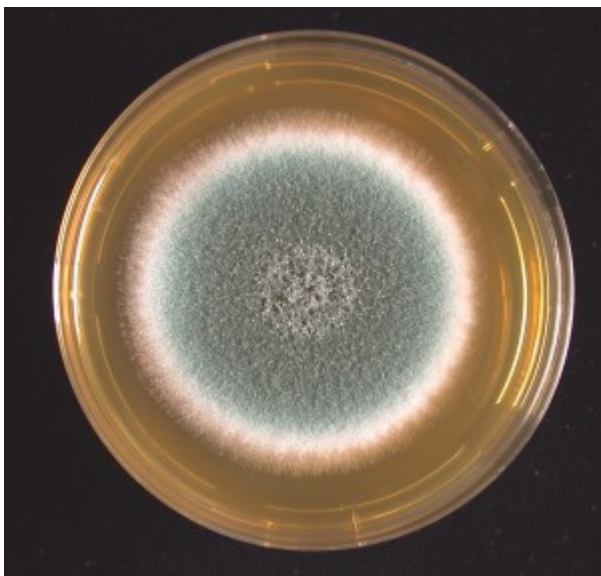


Fig. 5a. Haematoxylin and Eosin stained section of a retrobulbar fungal granuloma consisting of a large central granuloma surrounded by smaller satellite granulomas. Centrally each granuloma contains necrotic cellular debris within which branching, septate fungal hyphae are

*confined as seen on the Grocott stained section*



*Fig. 5b. There are surrounding zones of neutrophils and eosinophils, macrophages, fibroblasts and a peripheral cuff of lymphocytes and plasma cells (courtesy of Vanessa Barrs, University Veterinary Teaching Hospital, Sydney, Australia).*



*Fig. 6a. Growth of Aspergillus fumigatus on malt extract agar (MEA). Colonies are typically olive green and velvety due to rapid sporulation. Courtesy of Vanessa Barrs, University Veterinary Teaching Hospital, Sydney, Australia.*



*Fig. 6b. Some species of Aspergillus in the fumigatus complex that cause sino-orbital aspergillosis are slow to sporulate and the colonies appear whitish until sporulation occurs. Courtesy of Vanessa Barrs, University Veterinary Teaching Hospital, Sydney, Australia.*

Laboratory (haematology and serum biochemistry) abnormalities in cats with aspergillosis are not specific and reflect chronic inflammation. Hyperglobulinaemia is the most frequently reported abnormality (Hamilton et al., 2000; McLellan et al., 2006; Smith and Hoffman, 2010; Barrs et al., 2012).

### *Diagnostic imaging*

Advanced imaging techniques (CT or MRI) are helpful to assess disease extension and to find the best location for obtaining diagnostic samples during rhinoscopy (Fig. 7) or for CT-guided orbital biopsies (Whitney et al., 2005; Smith and Hoffman, 2010).



*Fig. 7. Rhinoscopy picture of a cat with sinonasal aspergillosis. Courtesy of Bianka Schulz, Medizinische Kleintierklinik, Ludwig-Maximilians-Universität München, Germany.*

CT and MRI are also important tools to rule out neoplasia. However, in a study including ten cats with fungal rhinitis (five with aspergillosis), CT findings did not allow discrimination between different fungal infections nor distinguish aspergillosis from neoplasia (Karnik et al., 2009).

Common CT findings in SNA and SOA include asymmetric, bilateral involvement of the nasal cavity, soft-tissue attenuation of the nasal cavity and sinuses, turbinate lysis, orbital bone lysis and other paranasal bone lysis and/or sclerosis. SOA is differentiated from SNA by the presence of a rostral and ventromedial orbital mass, which usually extends laterally into the paranasal maxillary soft-tissues and ventrally into the oral cavity (Barrs et al., 2014). Enhancement of orbital masses after contrast administration is heterogeneous and characterised by central hypoattenuating foci (necrotic areas) with peripheral enhancement (Barrs et al., 2014). Mineralisation of fungal metabolites, occasionally results in the presence of sinoliths or rhinoliths (Tomsa et al., 2003; Barrs et al., 2014).

### *Microscopic detection of the organism*

A definitive diagnosis is usually obtained by cytological or histological detection of branched, septate hyphae (2 – 5 µm diameter) in biopsy specimens obtained by rhinoscopy (Fig. 8), nasal cavity lavage techniques, or biopsy of orbital masses.



*Fig. 8. Rhinoscopy procedure in a cat with chronic nasal discharge to obtain samples for histology and culture of *Aspergillus* spp. Courtesy of Bianka Schulz, Medizinische Kleintierklinik, Ludwig-Maximilians-Universität München, Germany.*

In cats with non-invasive SNA, fungal plaques adhere to, but do not invade the mucosa of the nasal cavity and/or sinuses. Mucosal fungal plaques seen on rhinoscopy or sinuscopy should be biopsied for histopathology and fungal culture. In cats with SOA, fungal hyphae can be detected in orbital granulomas (Fig. 5), which can be accessible in some cases *via* biopsy of masses extending into the oral cavity (Fig. 3). Special histological stains, such as PAS or Grocott's silver stain, improve the sensitivity of detection of fungal hyphae. Identification of the *Aspergillus* species on the basis of microscopy is not possible.

### *Fungal culture*

The *Aspergillus* species that cause feline aspergillosis can usually be cultured readily on commercial fungal agars such as Sabouraud's or malt extract agar. *Aspergillus* species form mycelia with clearly visible conidia on conidiophores. Some species, such as *Aspergillus fumigatus*, sporulate rapidly (within five to seven days), while others, such as *Aspergillus felis*, are slower (Fig. 9). A single positive culture from swabs or secretions without histological evidence is not diagnostic, as the organism is ubiquitous.

Identification of *Aspergillus* species on the basis of fungal culture morphology is inaccurate. However, *Aspergillus fumigatus* is thermo-tolerant and can be differentiated from other closely related species by its ability to grow at 50 °C.



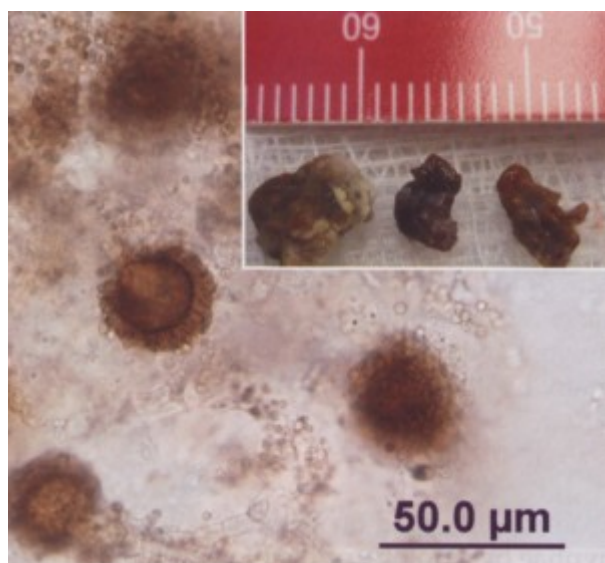


Fig. 9. *Aspergillus fumigatus* conidial heads from a squash preparation of fungal plaques (inset) in a Scottish shorthair cat with sinonasal aspergillosis. Courtesy of Vanessa Barrs, University Veterinary Teaching Hospital, Sydney, Australia.

## Polymerase chain reaction

For definitive identification of the *Aspergillus* species, such as *Aspergillus felis*, *Aspergillus fumigatus*, and *Aspergillus udagawae*, PCR is required. Pan-fungal PCR that amplifies conserved genes present in all fungi, such as the ribosomal RNA gene complex, can be applied to fungal culture material. If this is not available, formalin-fixed paraffin embedded tissues can be used (Barrs et al., 2013; Meason-Smith et al., 2017).

## Detection of fungal antigens or antibodies

Tests are available for detection of the fungal cell-wall antigen galactomannan (GM) or of detection of *Aspergillus* antibodies. Diagnostic utility of antibody as well as antigen tests in humans or animals with aspergillosis is affected by host immunocompetence. In DIA, which generally affects immunocompromised patients, serum antibody detection has a low sensitivity due to a frequently weak or undetectable antibody response. In these patients, serum GM detection is usually a more sensitive test (Pfeiffer et al., 2006; Garcia et al., 2012). By contrast, SNA and SOA usually occur in systemically immunocompetent cats that mount a robust humoral immune response. In one study, detection of *Aspergillus* species-specific IgG by ELISA was found to be both sensitive (95%) and specific (93%) for diagnosis of SNA and SOA in cats (Barrs et al., 2015). In the same study, detection of *Aspergillus* species antibodies in serum by agar gel immunodiffusion (AGID) was much less sensitive (43%), but highly specific (100%). Another type of immunodiffusion assay, counterimmunoelectrophoresis, has been used to detect *Aspergillus species* antibodies in cats with aspergillosis, but its diagnostic accuracy has not been evaluated so far (Tomsa et al., 2003). Serum GM tests are often negative in immunocompetent hosts due to antibody-antigen complexing or clearance from the circulation by neutrophils. In SOA and SNA, the sensitivity of GM detection is poor (23%), and testing is generally not useful for diagnosis (Taylor et al., 2016). In conclusion, antigen and antibody detection assays should be used as supportive, not as confirmatory, tests for the diagnosis of aspergillosis due to the possibility of false negative and false positive results.

## Treatment

No prospective controlled studies exist on the treatment of aspergillosis in cats, and available information is only based on retrospective case reports (table 2). In general, response to therapy and prognosis in SNA is good, when intensive and sufficiently long treatment is instituted. Response to treatment is less successful in invasive SOA, and prognosis is worse (Barrs et al., 2012). In systemic aspergillosis, prognosis is generally poor.

In non-invasive SNA, the principles of treatment are the same as for canine SNA. This includes endoscopic debridement of mucosal

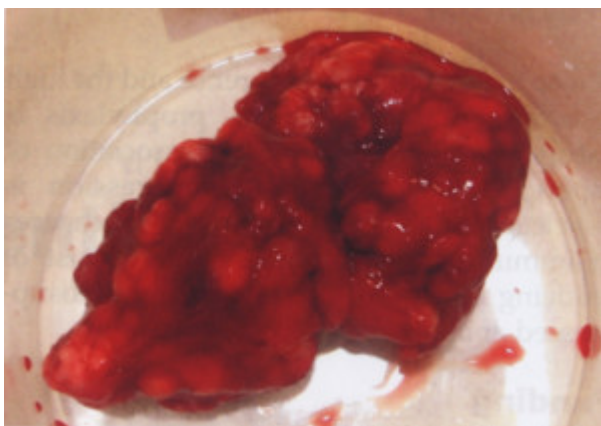
fungal plaques and local therapy, using clotrimazole or enilconazole intranasal infusions under general anesthesia (Fig 10) (Tomsa et al., 2003; Furrow and Groman, 2009; Tamborini et al., 2016).



*Fig. 10. Local infusion of clotrimazole under general anesthesia in a cat with sinonasal aspergillosis. Courtesy of Bianka Schulz, Medizinische Kleintierklinik, Ludwig-Maximilians-Universität München, Germany.*

A single intranasal infusion of clotrimazole led to long-term resolution of clinical signs in two studies, involving three cats (Tomsa et al., 2003) and two cats (Furrow and Groman, 2009). As with canine SNA, repeated endoscopic debridement and topical azole therapy can be required on one or more occasions to effect a cure (Tamborini et al., 2016). In cases in which topical azole treatment fails or is not possible (e.g., cribriform plate is not intact), systemic antifungal treatment should be given (itraconazole, posaconazole, terbinafine, or amphotericin B). Systemic antifungal treatment should be administered over several months, and owners should be informed early about the long treatment required. Based on case series, best choices for systemic treatment are itraconazole (5 mg/kg q 12 h PO) alone or in combination with amphotericin B, or the newer azole posaconazole (15 mg/kg loading dose PO, followed by 7.5 mg/kg q 24 h PO) (Mawby et al., 2016). Systemic treatment solely without fungal plaque debridement and local azole infusions is not as successful. Four cats with fungal rhinitis were treated with itraconazole orally; when therapy was discontinued, clinical signs recurred (Whitney et al., 2005).

In SOA, treatment is more difficult. Prognosis is poor even with aggressive treatment, including surgical debridement of orbital masses (exenteration) combined with systemic antifungal therapy (Fig. 11).



*Fig. 11. Retrobulbar granuloma after radical orbital debridement surgery. Courtesy of Vanessa Barrs, University Veterinary Teaching Hospital, Sydney,*

*Australia.*

In the largest cases series of twelve cats with SOA for which treatment outcomes could be assessed, all cats were treated with a systemic triazole (itraconazole, posaconazole, or voriconazole) alone or in combination with amphotericin B and/or terbinafine, and five cats also had orbital exenteration (Barrs et al., 2012). Treatment was successful in only one case, which did not have surgery. In that case, infection relapsed 19 months after treatment was stopped, but resolved after further therapy with caspofungin and posaconazole. In other reports of six cases of SOA that responded to systemic antifungal therapy, three of these also had surgical debridement of orbital granulomas, and orbital tissues of one were lavaged at surgery with 1% voriconazole (Hamilton et al., 2000; McLellan et al., 2006; Smith and Hoffman, 2010). Drug regimens suggested for treatment of SOA include posaconazole or itraconazole as monotherapy or in combination with terbinafine and/or amphotericin B for at least six months (McLellan et al., 2006; Barrs et al., 2012; Kano et al., 2013; Frey et al., 2016). Since *Aspergillus felis* and *Aspergillus udagawae*, the most common agents of SOA, can have high minimum inhibitory concentrations of azoles and amphotericin B, antifungal susceptibility testing of isolates is recommended to guide therapy (Barrs et al., 2013). Voriconazole is currently not recommended since its pharmacokinetics have not been determined in cats, and severe adverse neurological effects, including ataxia, paraplegia, and cranial nerve deficits have been reported (Quimby et al., 2010). In other mammals, voriconazole shows non-linear pharmacokinetics, and neurotoxicity can occur in association with high plasma voriconazole levels (Dolton et al., 2012).

If only the cornea is involved, local treatment alone can be successful. An 8-year-old cat that suffered from ulcerative keratitis with stromal loss, stromal infiltrate, corneal oedema, perilimbal vascularization, and miosis was treated with 1% voriconazole solution, and the keratomycosis resolved successfully (Labelle et al., 2009).

Although associated with a poor prognosis, one cat with pulmonary aspergillosis was successfully managed with a combination of surgery (lung lobectomy and chest drainage) and systemic itraconazole therapy for one month.

**Table 2. Treatment options for feline aspergillosis**

DRUG	DOSE	COMMENTS
Clotrimazole	1% solution in polyethylene glycol	Single or multiple intranasal local instillation; should be performed under general anaesthesia
Itraconazole	5 mg/kg q 12 h PO (capsules); 3 mg/kg q 12 h PO (oral suspension)	Suggested drug of choice for SNA after local treatment (should be given for at least 2-3 months, or 1 month beyond clinical cure). Capsules should be administered with food.
Posaconazole	7.5 mg/kg q 12 h PO	An initial loading dose of 15 mg/kg can be administered. Is available as oral suspension (40 mg/ml). Should be administered with food.
Terbinafine	30 mg/kg q 24 h PO	Adverse effects include anorexia, vomiting/diarrhoea, and facial pruritis resulting in excoriations.
Amphotericin B deoxycholate	0.5 mg/kg 2 times weekly SC	Should be administered in 350 ml 0.45% NaCl/2.5% dextrose over 2 (to 3) times weekly. Can be given to a cumulative dose of 10-15 mg/kg. A 5 mg/ml stock solution should be prepared, which can be stored frozen. Monitoring of urea/creatinine for nephrotoxicity is recommended. Drug should be discontinued for 2-3 weeks, if cat becomes azotemic.
Liposomal amphotericin	1 mg/kg q 48 h IV	Should be administered as a 1-2 mg/ml solution in 5% dextrose by IV infusion over 1-2 h. Dosage can be increased to 1.5 mg/kg.
Amphotericin B lipid complex	1 mg/kg 3 times weekly IV	Should be administered as a 1 mg/ml solution in 5% dextrose by IV infusion over 1-2 h.
Caspofungin acetate	0.75 mg/kg q 24 h IV	Should be administered as a 0.2 mg/ml solution in 0.9% NaCl by IV infusion over 1-2 h.

## Prevention

Due to the ubiquitous occurrence of *Aspergillus* species, prophylaxis is hardly possible. Although an association of aspergillosis with immunosuppression is not clearly established, prophylactic measures in immunocompromised animals consist of reducing exposure, for example restricting access to mouldy environments, such as garden compost heaps or mouldy bathrooms. It is recommended that immunosuppressed animals should be kept indoors, however, this measure alone cannot prevent aspergillosis, since *Aspergillus* species conidia are dispersed in air.

## Public health considerations

There are no public health issues concerning infected cats due to the ubiquitous occurrence of *Aspergillus* species.

## References

- Adamama-Moraitou KK, Paitaki CG, Rallis TS, Tontis D (2001): *Aspergillus* species cystitis in a cat. *J Feline Med Surg* 3, 31-34.
- Barachetti L, et al (2009): Bilateral orbital and nasal aspergillosis in a cat. *Vet Ophthalmol* 12, 176-182.
- Barrs VR, Talbot JJ (2014): Feline aspergillosis. *Vet Clin North Am Small Anim Pract* 44, 51-73.
- Barrs VR, et al (2012): Sinonasal and sino-orbital aspergillosis in 23 cats: aetiology, clinicopathological features and treatment outcomes. *Vet J* 191, 58-64.
- Barrs VR, et al (2013): *Aspergillus felis* sp. nov., an emerging agent of invasive aspergillosis in humans, cats, and dogs. *PLoS One* 8, e64871.
- Barrs VR, et al (2014): Computed tomographic features of feline sino-nasal and sino-orbital aspergillosis. *Vet J* 201, 215-222.
- Barrs VR, et al (2015): Detection of *Aspergillus*-specific antibodies by agar gel double immunodiffusion and IgG ELISA in feline upper respiratory tract aspergillosis. *Vet J* 203, 285-289.
- Burk RL, Joseph R, Baer K (1990): Systemic aspergillosis in a cat. *Vet Radiol* 31, 26-28.
- Davies C, Troy GC (1996): Deep mycotic infections in cats. *J Amer Animal Hosp Assoc* 32, 380-391.
- Declercq J, Declercq L, Fincioen S (2012): Unilateral sino-orbital and subcutaneous aspergillosis in a cat. *Vlaams Diergeneesk Tijdschr* 81, 357-362.
- Dolton MJ, et al (2012): Multicenter study of voriconazole pharmacokinetics and therapeutic drug monitoring. *Antimicrob Agents Chemother* 56, 4793-4799.
- Frey KG, et al (2016): Bioinformatic Characterization of Mosquito Viromes within the Eastern United States and Puerto Rico: Discovery of Novel Viruses. *Evol Bioinform Online* 12 (Suppl 2), 1-12.
- Furrow E, Groman RP (2009): Intranasal infusion of clotrimazole for the treatment of nasal aspergillosis in two cats. *J Amer Vet Med Assoc* 235, 1188-1193.
- Garcia RS, et al (2012): Sensitivity and Specificity of a Blood and Urine Galactomannan Antigen Assay for Diagnosis of Systemic Aspergillosis in Dogs. *J Vet Intern Med* 26, 911-919.
- Giordano C, et al (2010): Invasive mould infections of the naso-orbital region of cats: a case involving *Aspergillus fumigatus* and an aetiological review. *J Feline Med Surg* 12, 714-723.
- Goodale EC, Outerbridge CA, White SD (2016): *Aspergillus* otitis in small animals – a retrospective study of 17 cases. *Vet Dermatol* 27, 3-e2.
- Hamilton HL, Whitley RD, McLaughlin SA (2000): Exophthalmos secondary to aspergillosis in a cat. *J Amer Anim Hosp Assoc* 36, 343-347.
- Hazell KLA, Swift IM, Sullivan N (2011): Successful treatment of pulmonary aspergillosis in a cat. *Austral Vet J* 89, 101-104.
- Kano R, et al (2008): Isolation of *Aspergillus udagawae* from a fatal case of feline orbital aspergillosis. *Mycoses* 51, 360-361.
- Kano R, et al (2013): Two cases of feline orbital aspergillosis due to *A. udagawae* and *A. viridinutans*. *J Vet Med Sci* 75, 7-10.
- Kano R, et al (2015): The first case of feline sinonasal aspergillosis due to *Aspergillus fischeri* in Japan. *J Vet Med Sci* 77, 1183-1185.

- Karnik K, et al (2009): Computed tomographic findings of fungal rhinitis and sinusitis in cats. *Vet Radiol Ultrasound* 50, 65-68.
- Katz ME, et al (2005): Multiple genetically distinct groups revealed among clinical isolates identified as atypical *Aspergillus fumigatus*. *J Clin Microbiol* 43, 551-555.
- Labelle AL, et al (2009): *Aspergillus flavus* keratomycosis in a cat treated with topical 1% voriconazole solution. *Vet Ophthalmol* 12, 48-52.
- Malik R, et al (2004): Infections and some other conditions affecting the skin and subcutis of the naso-ocular region of cats - clinical experience 1987-2003. *J Feline Med Surg* 6, 383-390.
- Mawby DI, et al (2016): Posaconazole Pharmacokinetics in Healthy Cats after Oral and Intravenous Administration. *J Vet Intern Med* 30, 1703-1707.
- McLellan GJ, et al (2006): Use of posaconazole in the management of invasive orbital aspergillosis in a cat. *J Amer Anim Hosp Assoc* 42, 302-307.
- Meason-Smith C, et al (2017): Panfungal Polymerase Chain Reaction for Identification of Fungal Pathogens in Formalin-Fixed Animal Tissues. *Vet Pathol* 54, DOI: 300985817698207.
- Miller JS, et al (2011): Outcomes of the 2011 Botanical Nomenclature Section at the XVIII International Botanical Congress. *Phytokeys* 5, 1-3.
- Ossent P (1987): Systemic aspergillosis and mucormycosis in 23 cats. *Vet Rec* 120, 330-333.
- Peeters D, Clercx C (2007): Update on canine sinonasal aspergillosis. *Vet Clinics North America-Small Anim Practice* 37, 901-916.
- Pfeiffer CD, Fine JP, Safdar N (2006): Diagnosis of invasive aspergillosis using a galactomannan assay: A meta-analysis. *Clin Infect Dis* 42, 1417-1427.
- Pilton JL, et al (2014): Atypical, abscessated nasopharyngeal polyp associated with expansion and lysis of the tympanic bulla. *J Feline Med Surg* 16, 699-702.
- Quimby JM, et al (2010): Adverse Neurologic Events Associated with Voriconazole Use in 3 Cats. *J Vet Intern Med* 24, 647-649.
- Schulz B, et al (2007): Diagnostik und Therapie der nasalen Aspergillose bei der Katze - Fallbeschreibung und Literaturübersicht. *Tierärztl Prax* 35, 281-286.
- Sharp NJH, Harvey CE, Sullivan M (1991): Canine nasal aspergillosis and penicilliosis. *Comp Contin Educ Pract Vet* 13, 41-46.
- Smith LN, Hoffman SB (2010): A case series of unilateral orbital aspergillosis in three cats and treatment with voriconazole. *Vet Ophthalmol* 13, 190-203.
- Sugui JA, et al (2014): Genetic Relatedness versus Biological Compatibility between *Aspergillus fumigatus* and Related Species. *J Clin Microbiol* 52, 3707-3721.
- Stokes R (1973): Letter: Intestinal mycosis in a cat. *Austr Vet J* 49, 499-500.
- Tamborini A, et al (2016): Sinonasal aspergillosis in a British Shorthair cat in the UK. *J Feline Med Surg Open Reports* 1, 1-6.
- Taylor A, et al (2016): Evaluation of Serum *Aspergillus*-Specific Immunoglobulin A by Indirect ELISA for Diagnosis of Feline Upper Respiratory Tract Aspergillosis. *J Vet Intern Med* 30, 1708-1714.
- Tomsa K, et al (2003): Fungal rhinitis and sinusitis in three cats. *J Amer Vet Med Assoc* 222, 1380-1384.
- Whitney BL, Broussard J, Stefanacci JD (2005): Four cats with fungal rhinitis. *J Feline Med Surg* 7, 53-58.
- Wilkinson GT, Sutton RH, Grono LR (1982): *Aspergillus* spp infection associated with orbital cellulitis and sinusitis in a cat. *J Small Anim Pract* 23, 127-131.